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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
SCHWARTZMAN, R	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 02/21/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Advisory Action

Application No.	Applicant(s)
08/955,373	Mouritsen et al.
Examiner	**Group Art Unit**
Ron Schwadron, Ph.D.	1644

THE PERIOD FOR RESPONSE: [check only a) or b)]

a) ☐ expires _____ months from the mailing date of the final rejection.

b) ☐ expires either three months from the mailing date of the final rejection, or on the mailing date of this Advisory Action, whichever is later. In no event, however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☒ Appellant's Brief is due two months from the date of the Notice of Appeal filed on 11/2/2000 (or within any period for response set forth above, whichever is later). See 37 CFR 1.191(d) and 37 CFR 1.192(a).

Applicant's response to the final rejection, filed on 10/16/2000 has been considered with the following effect, but is NOT deemed to place the application in condition for allowance:

☒ The proposed amendment(s):

☒ will be entered upon filing of a Notice of Appeal and an Appeal Brief.

☐ will not be entered because:

☐ they raise new issues that would require further consideration and/or search. (See note below).

☐ they raise the issue of new matter. (See note below).

☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: _____

☐ Applicant's response has overcome the following rejection(s):

_____

☐ Newly proposed or amended claims _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claims.

☒ The affidavit, exhibit or request for reconsideration has been considered but does NOT place the application in condition for allowance because: See enclosed note

☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

☒ For purposes of Appeal, the status of the claims is as follows (see attached written explanation, if any):

Claims allowed: None

Claims objected to: N/A

Claims rejected: 26, 28, 45-47, 49, 50, 53

☐ The proposed drawing correction filed on _____ ☐ has ☐ has not been approved by the Examiner.

☐ Note the attached Information Disclosure Statement(s), PTO-1449, Paper No(s). _____.

☒ Other See enclosed note

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP 1800 1600

6. Claims 26,28,45-47,49,50,53 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

Claim 26 is indefinite in the recitation of "essentially preserve the overall tertiary structure" because it is unclear what this means or encompasses. It is unclear what changes to the tertiary structure would or would not be encompassed by the aforementioned term. For example, it is unclear if this term encompasses changes at the physical/chemical level (eg. crystal structured) or simply functional changes (eg. still immunogenic antigen as evidenced by antibody binding by antibodies specific for unmodified antigen). If the term is interpreted as encompassing changes at the physical/chemical level, it is unclear as to what deviations from the normal crystal structure would or would not be encompassed by the term "essentially preserve the overall tertiary structure".

Regarding applicants comments, the MPEP section 2173.02(Rev. 1, Feb 2000) states:

Clarity and Precision

The examiner's focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C. 112, second paragraph is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available. When the examiner is satisfied that patentable subject matter is disclosed, and it is apparent to the examiner that the claims are directed to such patentable subject matter, he or she should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness. Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire. Examiners are encouraged to suggest claim language to applicants to improve the clarity or precision of the language used, but should not reject claims or insist on their own preferences if other modes of expression selected by applicants satisfy the statutory requirement.

The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and

particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:

(A) The content of the particular application disclosure;

(B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

If the scope of the invention sought to be patented cannot be determined from the language of the claims with a reasonable degree of certainty, a rejection of the claims under 35 U.S.C. 112, second paragraph is appropriate. In re Wiggins, 488 F.2d 538, 179 USPQ 421 (CCPA 1973).

In the instant rejection *the scope of the invention sought to be patented cannot be determined from the language of the claims with a reasonable degree of certainty*, It is unclear what changes to the tertiary structure would or would not be encompassed by the aforementioned term. For example, it is unclear if this term encompasses changes at the physical/chemical level (eg. crystal structured) or simply functional changes (eg. still immunogenic antigen as evidenced by antibody binding by antibodies specific for unmodified antigen). If the term is interpreted as encompassing changes at the physical/chemical level, it is unclear as to what deviations from the normal crystal structure would or would not be encompassed by the term "essentially preserve the overall tertiary structure". Regarding applicants comments, said comments do not clarify what the term "essentially preserve the overall tertiary structure" means or encompasses. In light of applicants comments it is still unclear what this means or encompasses. Regarding applicants comments about said term and preserving B cell epitopes, it is unclear what changes to the tertiary structure would or would not be encompassed by the aforementioned term. For example, it is unclear if this term encompasses changes at the physical/chemical level (eg. crystal structured) or simply functional changes (eg. still immunogenic antigen as evidenced by antibody binding by antibodies specific for unmodified antigen). If the term is interpreted as encompassing changes at the physical/chemical level, it is unclear as to what deviations from the normal crystal structure would or would not be encompassed by the term "essentially preserve the overall tertiary structure".

It is suggested that applicant address this issue by filing a CPA or RCE and adopting language which does not use the aforementioned phrase (eg. proposed claim 55). The Examiner is not stating that proposed claim 55 would not necessarily raise new issues under 35 USC 112 first paragraph.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 26,28,45,46 stand rejected under 35 U.S.C. 102(b) as being anticipated by Russell-Jones et al. (WO 92/05192) for the reasons elaborated in the previous Office Action. Applicants arguments have been considered an deemed not persuasive.

Russell-Jones et al. teach T cell epitopes derived from Trat protein (see Abstract). Russell-Jones et al. teach Trat T cell epitopes are inserted into proteins, wherein the insertion of said peptide increases the antibody response against the protein into which Trat has been inserted (see page 4, lines 24-26 and Abstract). Russell-Jones et al. teach that the Trat peptide is inserted such that the protein still functions as an immunogen. The Trat peptide has been inserted into the immunogen in such a manner as to "essentially preserve the overall tertiary structure", because the ability of the immunogen to function as an immunogen is maintained (see page 8, first complete paragraph). Russell-Jones et al. teach that the Trat modified immunogen can be used as a vaccine in a composition containing an adjuvant such as saponin (see page 8 and 13). Russell-Jones et al. teach that using recombinant DNA technology that Trat peptide can be inserted into the immunogen via substituting Trat peptide for a peptide contained in said molecule (see page 32 and page 31, first incomplete paragraph). Said insertion would preserve flanking regions on both sides of the Trat T cell epitope. The Trat peptide has been inserted into the immunogen in such a manner as to "essentially preserve the overall tertiary structure", because the ability of the immunogen to function as an immunogen is maintained. Russell-Jones et al. teach that immunogens used in the aforementioned vaccines can include self

proteins such as luteinizing hormone, somatostatin, inhibin, FSH (see page 9 and claim 12). Russell-Jones et al. teach that such vaccines can be used in animals and humans.

Regarding the Travers declaration, paragraph 11 states that to the best of his knowledge that mammalian self proteins do not contain suppressor regions. However, mammalian proteins containing suppressor regions/epitopes are well known in the art (see Miller et al. abstract and Parkar et al. abstract). Thus, not only are mammalian proteins containing suppressor regions/epitopes well known in the art, the aforementioned also indicates that Travers is not an expert in the particular technology relevant to the claimed invention (eg. he is not familiar with the relevant prior art).

Regarding applicants comments about "self proteins", Russell-Jones et al. teaches that the claimed invention can be used as a vaccine in humans (see page 33) and can be used to raise antibody responses against such proteins as luteinizing hormone, somatostatin, inhibin, FSH (eg. self proteins). There is no teaching in Russell-Jones et al. that humans would be immunized with nonhuman modified luteinizing hormone, somatostatin, inhibin or FSH. The Talwar et al. abstract submitted by applicant actually discloses use of human hCG conjugated to TT. In addition, the specification, page 2, lines 22-24 discloses that Talwar et al., 1992 disclose the use of human hCG/tetanus toxoid as a vaccine in humans. Thus, use of human derived molecules in vaccines for humans was known in the art. Furthermore, the teachings of Russell-Jones et al. are not limited to methods of making immunogenic molecules more immunogenic. Russell-Jones et al. teach that, "The at least one "immunogen" which forms part of the complex *is any molecule which it is desirable to use to raise an immune response.*". Thus, Russell-Jones et al. are using the term "immunogen" to include molecules that are potentially immunogenic when conjugated to Trat. Furthermore, regarding the term "immunogen", virtually any self molecule is an immunogen if administered to another species of animal or if administered to the animal from which it was derived wherein it is administered with an appropriate adjuvant. Regarding applicants comments about insertion versus substitution, Russell-Jones et al. teach that it would be within the skill of a routineer to produce modified fusion proteins wherein Trat was included and wherein the fusion protein still had the activity of the parent molecule (see page 9). The teachings of Russell-Jones et al. are not limited to Trat insertion versus substitution and page 32 provides an example that would be

applicable to any antigen. Russell-Jones et al. clearly teach substitution of Trat for amino acid sequences found in a nonTrat molecule (see page 32). Furthermore, the teachings of page 32 are not limited to GP120 ("Using recombinant DNA technology, the "suppressor regions" in a *number of prospective vaccine proteins* including gp 120 ..."). Regarding applicants comments about whether Example 5 is enabled or not enabled, applicant has provided no evidence that said Example is not enabled. Furthermore, even if "suppressor regions" had no effect on immune responses, the Example would be no different the claimed invention, which merely discloses insertion of a exogenous T cell epitope into a molecule. Regarding applicants comments about "essentially preserve the overall tertiary structure", the Trat peptide has been inserted into the immunogen in such a manner as to "essentially preserve the overall tertiary structure", because the ability of the immunogen to function as an immunogen is maintained (see page 8, first complete paragraph). Furthermore, there is no disclosure in the specification as to what "essentially preserve the overall tertiary structure" means or encompasses, and there is no disclosure as to what changes to tertiary structure or degrees of change would or would not encompass changes that "essentially preserve the overall tertiary structure". Regarding applicants comments about whether Example 5 is enabled or not enabled, applicant has provided no evidence that said Example is not enabled.

Regarding applicants comments about species anticipation by a genius, the MPEP section 2131.02 teaches that a genus anticipates a species if the genus consists of a small number of species that are "at once envisaged" from the genus. The MPEP section 2131.02 (Rev. 1, Feb. 2000) teaches that:

A GENERIC CHEMICAL FORMULA WILL ANTICIPATE A CLAIMED SPECIES COVERED BY THE FORMULA WHEN THE SPECIES CAN BE "AT ONCE ENVISAGED" FROM THE FORMULA

When the compound is not specifically named, but instead it is necessary to select portions of teachings within a reference and combine them, e.g., select various substituents from a list of alternatives given for placement at specific sites on a generic compound were anticipated because the prior art taught a generic formula embracing a limited number of compounds closely related to each other in structure and the properties

possessed by the compound class of the prior art was that disclosed for the claimed compound. The broad generic formula seemed to describe an infinite number of compounds but claim 1 was limited to a structure with only one variable substituent R. This substituent was limited to low alkyl radicals. One of ordinary skill in the art would at once envisage the subject matter within claim 1 of the reference.). chemical formula to arrive at a specific composition, anticipation can only be found if the classes of substituents are sufficiently limited or well delineated. Ex parte A, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990). If one of ordinary skill in the art is able to "at once envisage" the specific compound within the generic chemical formula, the compound is anticipated. One of ordinary skill in the art must be able to draw the structural formula or write the name of each of the compounds included in the generic formula before any of the compounds can be "at once envisaged." One may look to the preferred embodiments to determine which compounds can be anticipated. In re Petering, 301 F.2d 676, 133 USPQ 275 (CCPA 1962).

In In re Petering, the prior art disclosed a generic chemical formula "wherein X, Y, Z,

P, and R4- represent either hydrogen or alkyl radicals, R a side chain containing an OH group." The court held that this formula, without more, could not anticipate a claim to 7-methyl-9-[d, l4-ribityl]-isoalloxazine because the generic formula encompassed a vast number and perhaps even an infinite number of compounds. However, the reference also disclosed preferred substituents for X, Y, Z, R, and R' as follows: where X, P, and R' are hydrogen, where Y and Z may be hydrogen or methyl, and where R is one of eight specific isoalloxazines. The court determined that this more limited generic class consisted of about 20 compounds. The limited number of compounds covered by the preferred formula in combination with the fact that the number of substituents was low at each site, the ring positions were limited, and there was a large unchanging structural nucleus, resulted in a finding that the reference sufficiently described "each of the various permutations here involved as fully as if he had drawn each structural formula or had written each name." The claimed compound was 1 of these 20 compounds. Therefore, the reference "described" the claimed compound and the reference anticipated the claims.

In In re Schauman, 572 F.2d 312, 197 USPQ 5 (CCPA 1978), claims to a specific compound were anticipated because the prior art taught a generic formula embracing a

limited number of compounds closely related to each other in structure and the properties possessed by the compound class of the prior art was that disclosed for the claimed compound. The broad generic formula seemed to describe an infinite number of compounds but claim 1 was limited to a structure with only one variable substituent R. This substituent was limited to low alkyl radicals. One of ordinary skill in the art would at once envisage the subject matter within claim 1 of the reference.).

Compare In re Meyer, 599 F.2d 1026, 202 USPQ 175 (CCPA 1979) (A reference disclosing "alkaline chlorine or bromine solution" embraces a large number of species and cannot be said to anticipate claims to "alkali metal hypochlorite."); Akzo N.V. v. International Trade Comm 'n, 808 F.2d 1471, 1 USPQ2d 1241 (Fed. Cir. 1986) (Claims to a process for making aramid fibers using a 98% solution of sulfuric acid were not anticipated by a reference which disclosed using sulfuric acid solution but which did not disclose using a 98% concentrated sulfuric acid solution.). See MPEP § 2144.08 for a discussion of obviousness in genus-species situations.

Russell-Jones et al. teach that their invention encompasses vaccines for use in animals and humans (see page 33). Russell-Jones et al. teach that one such immunogen could include luteinizing hormone or somatostatin or FSH or inhibin (see page 9). Said proteins could only be of two different origins (human or nonhuman). Thus, based on the disclosure of Russell-Jones et al., one of ordinary skill in the art would at once envisage use of human self-protein as a vaccine as per page 33 of Russell-Jones. In addition, the specification, page 2, lines 22-24 discloses that Talwar et al., 1992 disclose the use of human hCG/tetanus toxoid as a vaccine in humans, indicating that the use of human self-proteins for human vaccines was already known in the art.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 26,28,45-47,49,50,53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Russell-Jones et al. (WO 92/05192) in view of Hellman (WO 93/05810), Etlinger and prior art disclosed in the specification (page 18, last paragraph).

Russell-Jones et al. teach T cell epitopes derived from Trat protein (see Abstract). Russell-Jones et al. teach Trat T cell epitopes are inserted into proteins, wherein the insertion of said peptide increases the antibody response against the protein into which Trat has been inserted (see page 4, lines 24-26 and Abstract). Russell-Jones et al. teach that the Trat peptide is inserted such that the protein still functions as an immunogen. The Trat peptide has been inserted into the immunogen in such a manner as to "essentially preserve the overall tertiary structure", because the ability of the immunogen to function as an immunogen is maintained (see page 8, first complete paragraph). Russell-Jones et al. teach that the Trat modified immunogen can be used as a vaccine in a composition containing an adjuvant such as saponin (see page 8 and 13). Russell-Jones et al. teach that using recombinant DNA technology that Trat peptide can be inserted into the immunogen via substituting Trat peptide for a peptide contained in said molecule (see page 32 and page 31, first incomplete paragraph). Said insertion would preserve flanking regions on both sides of the Trat T cell epitope. The Trat peptide has been inserted into the immunogen in such a manner as to "essentially preserve the overall tertiary structure", because the ability of the immunogen to function as an immunogen is maintained. Russell-Jones et al. teach that immunogens used in the aforementioned vaccines can include self proteins such as luteinizing hormone, somatostatin, inhibin, FSH (see page 9 and claim 12). Russell-Jones et al. teach that such vaccines can be used in animals and humans. Russell-Jones et al. do not teach the claimed method using TNFα. Hellman teaches that modulation of self proteins responsible for manifestations of a particular disease can be achieved using self-protein conjugated to a carrier which is recognized by T helper cells(see pages 5-12). The specification discloses that the role of TNFα in the pathogenesis of various diseases is known in the art (page 18, last paragraph). An antiTNF antibody produced by the claimed method would have been able to treat any TNF mediated disease. It would have been prima facies obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because the role of TNFα was known in the art, Hellman teaches that modulation of self proteins

responsible for manifestations of a particular disease can be achieved using self molecules that contain T helper epitopes and Russell-Jones et al. teach methods for inducing antibodies against self proteins using Trat modified molecules.

Regarding applicants comments about Hellman et al., the instant rejection states: "Hellman teaches that modulation of self proteins responsible for manifestations of a particular disease can be achieved using self-protein conjugated to a carrier which is recognized by T helper cells(see pages 5-12).". The teaching from Hellman doesn't relate to a "mutated form of the constant CH2-CH3 domains". Therefore, applicants comments related to this issue are irrelevant to the rejection under consideration.

10. No claim is allowed.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 1600 at (703) 305-3014.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Monday through Thursday from 7:30 to 6:00. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

Ron Schwadron, Ph.D.
Primary Examiner
Art Unit 1644